Assessing Preference-Based Outcome Measures for Overactive Bladder: An Evaluation of Patient-reported Outcome Data from the BESIDE Clinical Trial

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ABSTRACT

Objectives

To compare outcomes using two preference-based measures of health status (EQ-5D-5L and OAB-5D) in patients with overactive bladder (OAB) treated with solifenacin plus mirabegron or solifenacin monotherapy in the BESIDE trial.

Methods

Patients with OAB remaining incontinent after 4 weeks' treatment with solifenacin 5 mg were randomized 1:1:1 to combination treatment (solifenacin 5 mg plus mirabegron [25 mg for the first 4 weeks/50 mg for the last 8 weeks]), solifenacin 5 mg, or solifenacin 10 mg. EQ-5D-5L and OAB-q were administered at baseline, weeks 4, 8, 12 and end of treatment (EoT). OAB-5D scores were derived from OAB-q results. Responder analysis was carried out using several definitions of minimally important difference.

Results

2054 patients received ≥1 dose of study treatment (combination, *n* = 694; solifenacin 5 mg, *n* = 684; solifenacin 10 mg, *n* = 676). EQ-5D-5L Index mean score changes (from baseline to EoT) were greater with combination (0.059) compared with solifenacin 5 mg (0.040) and 10 mg (0.044) monotherapy, but the differences were not statistically significant. A significantly greater improvement was observed for combination on OAB-5D (0.107 vs 0.085 for 5 mg and 0.087 for 10 mg; $p \leq 0.01$). The dimensions most improved overall were anxiety/depression, pain/discomfort and usual activities on EQ-5D-5L, and urge, urine loss and coping on OAB-5D. The

proportion of responders was significantly greater with combination compared with monotherapy using OAB-5D only.

Conclusions

Improvements were observed in all study arms on both the EQ-5D-5L and OAB-5D, although only the OAB-5D showed a statistically significant benefit for combination versus solifenacin monotherapy. Combining generic and condition-specific preference-based health status measures allows for assessment of dimensions which are particularly relevant to this patient population, while permitting comparison with outcomes from other studies, treatments and populations via EQ-5D.

Key points

- Both solifenacin alone and solifenacin plus mirabegron improve health-related quality of life after 12 weeks of treatment in patients with overactive bladder
- The improvement in health-related quality of life is significantly greater with solifenacin plus mirabegron compared with solifenacin alone
- Significant differences between the study arms was observed with the condition-specific measure of health-related quality of life (OAB-5D) but not the generic measure (EQ-5D-5L)

1 Introduction

Overactive bladder (OAB) is a common and debilitating condition, defined as urinary urgency with/without urgency urinary incontinence, usually with increased daytime frequency and nocturia in the absence of proven infection or other obvious pathology [1]. OAB symptoms compromise health-related quality of life (HRQoL) and negatively affect sleep quality, social activities, self-esteem, relationships, work productivity, physical exercise, psychological health, and sexual activity/enjoyment [2-5]. Among OAB symptoms, urgency urinary incontinence – present in approximately one-third of OAB cases – has the greatest negative impact on HRQoL and has a major socioeconomic impact [2,6].

Mirabegron is a selective β_3-adrenoreceptor agonist, which relaxes bladder smooth muscle and increases bladder storage capacity [7]. Multiple Phase III trials have demonstrated the efficacy and tolerability of this agent in patients with OAB [8-10], and mirabegron is indicated for the treatment of urgency, increased micturition frequency and/or urgency incontinence [11].

Antimuscarinic agents and mirabegron represent standard of care pharmacological treatment options for OAB. Although the two drug classes provide similar efficacy, mirabegron is not associated with bothersome, typical anticholinergic side effects such as dry mouth [12]. OAB is a chronic condition which often requires long-term management. The occurrence of anticholinergic side effects can potentially limit the use of antimuscarinics in patients among whom symptoms persist [13]. It is therefore of interest to investigate whether the addition of mirabegron, with its different mechanism of action, may improve OAB symptoms, without the need for

antimuscarinic dose escalation and potential concomitant increase in anticholinergic burden and adverse effects.

The evaluation of new medical treatments and technologies increasingly involves analysis of their cost-effectiveness and cost-utility – these analyses form an integral part of health technology assessment (HTA). In many countries, cost-utility analysis (CUA) can also be critical to decision-making on reimbursement. Within the CUA framework, preference-based measures (PBMs) of health status provide a multidimensional description of health to which societal preference weights (or utilities) can be attached. These preference weights can then be used in combination with survival data to generate quality-adjusted life-years [14]. One widely used PBM is the EQ-5D, a simple instrument measuring five dimensions of health status, which is the preferred measure of the National Institute for Health and Care Excellence in England/Wales [15]. Although of great value, generic PBMs (e.g., EQ-5D), which are applicable to a wide range of patient groups and conditions, may not capture all aspects of health status relevant to patients with a particular condition. In such cases, condition-specific PBMs are sometimes developed, e.g., the OAB-5D for patients with OAB [16]. Given that both EQ-5D and OAB-5D could potentially be used to generate utilities for OAB, and given the importance of CUA in HTA and treatment funding discussions, it is critical to understand how the two instruments perform comparatively.

The inclusion of the latest version of EQ-5D (i.e., EQ-5D-5L), which has five response levels for each of the five dimensions [17], and OAB-5D in a recent Phase III trial of OAB (BESIDE [18]) provided an opportunity for such a comparison within an exploratory analysis presented here. This was the first time that EQ-5D-5L

has been compared head-to-head with OAB-5D, and the first time that the new EQ-5D-5L value set for England has been reported in an OAB patient population.

2 Materials and Methods

2.1 Study Design and Patients

BESIDE was a randomized double-blind multicenter Phase IIIb trial (NCT01908829) that included multiple investigator sites in Europe, the United States, Canada, Australia and Lebanon; the methods have been published previously [18]. In brief, patients aged ≥18-years-old with OAB symptoms for >3 months, including an average of ≥2 incontinence episodes/24 hours, entered a 2-week screening/wash-out period to remove the effects of previous OAB medication and to familiarize with the patient-recorded electronic micturition diary. Patients then underwent 4-week single-blind treatment with solifenacin 5 mg/day. Patients still experiencing ≥1 incontinence episode during a 3-day diary were eligible for randomization (1:1:1) to 12 weeks of combination treatment (solifenacin 5 mg/day plus mirabegron 25 mg/day for 4 weeks then mirabegron 50 mg/day for the remaining 8 weeks), solifenacin 5 mg/day or 10 mg/day.

The primary publication reported that the combination significantly reduced daily incontinence episodes (primary endpoint; −1.80 versus −1.53, $p < 0.01$), daily micturitions (−1.59 versus −1.14, $p < 0.01$) and incontinence episodes over 3 days (4.25 versus 4.87, $p = 0.01$) compared with solifenacin 5 mg [18]. The combination was non-inferior to solifenacin 10 mg for both key secondary endpoints (daily micturitions [−1.59 versus −1.12, $p < 0.01$] and incontinence episodes over 3 days [4.25 versus 4.72, $p = 0.13$]) and superior to solifenacin 10 mg for daily

micturition[18]. In addition, the incidence of dry mouth with the combination was similar to solifenacin 5 mg [18].

2.2 Patient-reported outcome measures

The following patient reported outcome (PRO) measures were included in the BESIDE trial: the OAB questionnaire (OAB-q), from which OAB-5D preference-based scores can be derived; the patient perception of bladder condition (PPBC) questionnaire; the treatment satisfaction visual analog scale (TS-VAS); the patient and clinician global impression of change (PGIC and CGIC) scales; and the EQ-5D-5L. The analysis in the present paper reports on the EQ-5D-5L, OAB-5D, PGIC and CGIC; outcomes from the PPBC, TS-VAS and OAB-q are reported separately [19].

EQ-5D-5L measures health status in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [17]. Each dimension has five response levels (1 to 5): no problems, slight/mild problems, moderate problems, severe problems and extreme problems/unable to perform activity. Respondents are asked to indicate their health status on the day of administration by selecting the most appropriate response for each dimension. The 1-digit numbers for each dimension are then combined to provide a 5-digit descriptive profile of the respondent's overall health state. Societal preference weights generated using trade-off techniques are available in the form of a single index value for each of the 3125 possible EQ-5D-5L health states. In the current analysis, EQ-5D-5L index values were calculated using the recently developed value set for England [20,21], with scores which range from –0.281 (worst possible health state, i.e., 55555) to 1 (best possible health state/full health, i.e., 11111).

OAB-5D was derived from OAB-q – a 33-item condition-specific questionnaire that consists of an eight-item symptom bother scale and a 25-item health status utility measure scale [22]. OAB-5D is a reduced health state classification system that includes five dimensions (urge to urinate, urine loss, sleep impact, coping strategy, and concern with urinary problems) with five severity levels (ranging from 1 denoting no problem to 5 indicating an extreme problem) [16]. Like EQ-5D-5L, OAB-5D generates descriptive profiles representing 3125 unique health states which were translated into a single index value using trade off techniques in a representative sample of the UK population [23].

PGIC and CGIC evaluate health status using a simple seven-point single-item scale ranging from ‘very much improved’ to ‘very much worse’. On PGIC, each patient rated any change in his/her bladder symptoms and general health from baseline, whereas CGIC was rated by clinicians based on changes they observed in the patient's bladder symptoms.

Data for the EQ-5D-5L and OAB-5D questionnaires were collected at baseline, at weeks 4, 8 and 12, and end of treatment (EoT); PGIC and CGIC data were collected at EoT only.

2.3 Responder Analyses

Responder analyses were performed to determine the number and proportion of patients who achieved at least a minimally important difference (MID), or improvement, on EQ-5D-5L or OAB-5D. The MID can be defined as the smallest change that is perceived by patients as beneficial or that would result in a change in treatment [24]. However, there are multiple ways of estimating a MID and they usually give a range of possible values. There are no previously published MID

values for EQ-5D-5L or OAB-5D, and we used several approaches to estimating them for the present study. As there is no agreement on which method for estimating MIDs is the most appropriate for health status utility measures, such as those used here, we performed several responder analyses using the different MIDs derived for the current analysis. For EQ-5D-5L, a responder was defined by an incremental improvement from baseline to EoT of at least: (a) 0.017, i.e., the mean increment in patients who reported at least minimally improved health on the PGIC index; (b) 0.102, i.e., 0.5 standard deviation (SD) of the mean index value for the total study population at baseline; and (c) 0.065, i.e., mean change in utility associated with a one-level change in any dimension of the descriptive system (e.g., 11112 vs 11113) as described in Luo et al [25]. The same approaches were applied to OAB-5D, generating MIDs of: (a) 0.054; (b) 0.043; and (c) 0.020, respectively. In addition, double responder analyses were conducted for EQ-5D-5L and OAB-5D by combining the data for two definitions of MID described above, i.e. assessing the proportion of patients who achieved two MIDs (e.g. EQ-5D-5L ≥0.017 and OAB-5D ≥0.054).

2.4 Statistical Analyses

EQ-5D-5L and OAB-5D data were analyzed using a modified full analysis set (mFAS, defined as all randomized patients [after 4-week solifenacin run-in] who received ≥1 dose of double-blind treatment, had ≥1 micturition at and after baseline, had ≥1 incontinence episode at baseline, and completed the EQ-5D-5L questionnaire at baseline and at least once post-baseline). Patients with missing baseline EQ-5D-5L values were excluded; missing values at EoT were imputed using last observation carried forward. Analyses were also performed using a per protocol set (PPS), which included all patients in the mFAS except those meeting

additional exclusion criteria (Supplementary Table 1). Categorical variables were summarized by counts and percentages and compared between treatments by Chi-square tests, while mean (SD) and Student's t tests were used for continuous variables. Analysis of covariance (ANCOVA) models were used to compare changes in EQ-5D--5L and OAB-5D index scores from baseline to EoT, adjusting for the following covariates: baseline index score, sex, age, geographic region and 4-week incontinence reduction (yes/no). Spearman's correlation estimate analyses were performed between the PGIC and CGIC data and the EQ-5D-5L and OAB-5D index data.

3 Results

The mFAS included 2054 patients (combination, *n* = 694; solifenacin 5 mg, *n* = 684; solifenacin 10 mg, *n* = 676). Overall, 1902 patients comprised the PPS (combination, *n* = 631; solifenacin 5 mg, *n* = 640; solifenacin 10 mg, *n* = 631). Similar baseline demographic and clinical characteristics were observed across the three treatment arms in the mFAS (Table 1) and PPS.

3.1 EQ-5D-5L and OAB-5D indices

The mean change with EQ-5D-5L index from baseline to EoT was statistically significant for combination therapy (0.059; adjusted $p < 0.01$), solifenacin 5 mg (0.040; adjusted $p < 0.01$) and solifenacin 10 mg (0.044; adjusted $p < 0.01$) (Fig. 1A); the magnitude of change was not statistically significant for combination therapy versus solifenacin 5 mg (adjusted $p = 0.12$) and solifenacin 10 mg (adjusted $p = 0.11$). The proportion of patients with EQ-5D-5L scores indicating full health/no problems on any dimension (i.e., 11111 profile) increased at EoT (43–47 %) versus

baseline (29–30 %) and was similar across the three treatment arms (Supplementary Table 2).

Using OAB-5D, the improvement in health status from baseline to EoT was significantly greater with the combination (0.107; adjusted $p < 0.01$), solifenacin 5 mg (0.085; adjusted $p < 0.01$) and solifenacin 10 mg (0.087; adjusted $p < 0.01$) (Fig. 1B), and with the combination versus solifenacin 5 mg (adjusted $p < 0.01$) and solifenacin 10 mg (adjusted $p < 0.01$). The proportion of patients with OAB-5D scores reporting full health was greater at EoT (9–13 %) versus baseline (0–1 %) and was similar at both time points across the three treatment arms (Supplementary Table 2). The dimension score results based on the PPS were similar to mFAS (data not shown).

3.2 Questionnaire Dimensions: EQ-5D-5L and OAB-5D

The EQ-5D-5L dimensions showing most improvement in terms of the proportion of patients who switched from reporting problems at baseline to ‘no problems’ at EoT were anxiety/depression, pain/discomfort and usual activities. This finding was common to all three treatment arms (Fig. 2A). The proportion of patients reporting no problems in OAB-5D dimensions also increased from baseline to EoT in all three treatment arms (Fig. 2B); the largest improvements were observed for the combination treatment and were seen on the urge (3 % to 24 %), urine loss (3 % to 42 %) and coping (8 % to 36 %) dimensions.

3.3 PGIC and CGIC

The proportion of patients who reported their bladder symptoms as very much/much improved at EoT was higher in the combination group (73.9 %) versus solifenacin 5 mg (63.4 % [$p < 0.01$]) and solifenacin 10 mg (67.3 % [$p = 0.01$]) (Supplementary Table 3). Similar findings were reported for PGIC general health

(very much/much improved: 58.8 % vs 51.9 % [$p = 0.01$] and 52.0 % [$p = 0.01$]) and CGIC bladder symptoms (very much/much improved: 74.1 % vs 64.8 % [$p < 0.01$] and 69.0 % [$p = 0.03$]) with combination, solifenacin 5 mg and solifenacin 10 mg, respectively.

3.4 Responder Analyses

With EQ-5D-5L, no statistically significant differences in responder rates, according to all definitions of MID, were observed between any treatment arms (Table 2). In contrast, the combination group showed higher responder rates than solifenacin monotherapy according to all definitions of MID using OAB-5D (Table 2); no significant differences were observed between solifenacin 5 mg and 10 mg.

In the double responder analysis, the proportion of responders was significantly greater with the combination compared with both solifenacin arms using the EQ-5D-5L MID ≥0.017 and the OAB-5D MIDs ≥0.054 and ≥0.043 (all $p \leq 0.05$; Table 2). The proportion of responders for other combinations of MID definitions was numerically greater for the combination compared with solifenacin monotherapies, but the differences were not statistically significant.

3.5 Correlation of EQ-5D-5L and OAB-5D with PGIC and CGIC

In patients who reported very much/much improvement in PGIC bladder, the change in mean EQ-5D-5L index scores was numerically greater in the combination group compared with solifenacin 5 mg and 10 mg (0.072 vs 0.064 and 0.058, respectively). Similar changes in EQ-5D-5L index scores for combination versus monotherapy were observed in patients with very much/much improved PGIC general health (0.082 vs 0.067 and 0.068, respectively) and very much/much improved CGIC bladder (0.071 vs 0.062 and 0.052) (Supplementary Table 4). A similar pattern of

numerically higher OAB-5D index scores was observed with very much/much improved PGIC bladder (0.130 vs 0.118 and 0.112, respectively), PGIC general health (0.133 vs 0.118 and 0.115, respectively) and CGIC bladder (0.127 vs 0.111 and 0.108) (Supplementary Table 5). The Spearman's analysis showed a positive correlation ($p < 0.01$) between ratings on PGIC and EQ-5D-5L and OAB-5D (Supplementary Table 6).

4 Discussion

Consistent with earlier observations of significantly improved HRQoL via OAB-q, PPBC and TS-VAS in BESIDE [19], the present analysis shows that benefits were observed in the combination and solifenacin monotherapy arms at EoT compared with baseline using both the generic and condition-specific measures. These results complement the earlier published findings from the BESIDE trial which showed that the combination of solifenacin 5 mg plus mirabegron significantly improves symptoms of OAB compared with solifenacin monotherapy in incontinent OAB patients [18]. Most notably, the combination was superior to solifenacin 5 mg alone in improving symptoms of incontinence among patients who remained incontinent despite initial solifenacin 5 mg treatment [18].

The EQ Index and individual EQ-5D-5L dimensions showed no significant differences in the degree of change between study arms. A lack of significant difference between study arms on EQ-5D-3L (i.e., five dimensions with three levels) was also observed in a pooled analysis of three Phase III studies of mirabegron [26]. However, the magnitude of change in EQ-5D Index scores (from baseline to Week 12) in this earlier study (0.026–0.045) was similar to that observed in the present study (0.040–0.059). The fact that EQ-5D-5L is a generic instrument that measures

core dimensions of health status, which need to be relevant to a wide range of patient groups with differing severity/number of symptoms, may make it less sensitive to the type of between-arm differences observed in this OAB patient group. The high ceiling effect (29–30 % of patients reported full health at baseline) may have also reduced the instrument's ability to distinguish between groups or to fully capture changes over time.

In contrast, the condition-specific OAB-5D index was more sensitive to changes in health status than EQ-5D-5L and showed statistically significant differences between treatment arms. These findings are consistent with an earlier report of health-state utilities for patients with OAB, which evaluated both measures in a pooled analysis of three large, multicenter, placebo-controlled trials [27]. That the OAB-5D index is more sensitive than EQ-5D-5L for detecting changes in health status is not unexpected, as condition-specific instruments include items of more relevance to a particular condition and are likely to be less influenced by natural variation in health status unrelated to the specific condition.

Among OAB symptoms, urgency urinary incontinence is recognized as having the greatest negative impact on HRQoL [3]. The most notable improvements observed on OAB-5D in the present study were observed in the urge, urine loss and coping dimensions – this likely reflects the significant improvements in incontinence and micturition symptoms observed with the combination [18]. Together, the data are in consonance with the results from recent discrete choice experiments that showed patients with OAB have a preference for avoidance of urgency and incontinence episodes and reduction in micturition frequency [28,29], and suggest that

improvements captured by OAB-5D in the current study occurred to important dimensions that are likely of particular relevance to patients with OAB.

During the BESIDE trial, the combination treatment was well tolerated. In particular, the incidence of dry mouth – which is frequently reported with antimuscarinics and a common reason for treatment discontinuation – was lower with combination versus solifenacin 10 mg and similar to solifenacin 5 mg [16]. A treatment which maintains efficacy while constraining side effects is likely to show a greater advantage in terms of utility. Although we did not directly analyse the impact of dry mouth and other side effects in the present study, a recent publication showed that the side effects of antimuscarinic treatment (mainly dry mouth, but also constipation) can have a considerable negative impact on EQ-5D utilities [30].

For the combination treatment, the change in EQ-5D-5L scores from baseline to EoT (0.06) exceeded the threshold value for one of the three MIDs (i.e., 0.017 based on PGIC) and was approximately the same value as the MID calculated using the one-step transition methodology (i.e., 0.065), suggesting that the change observed on EQ-5D was meaningful [25]. While there were no statistically significant differences in the proportion of responders between the three treatment arms using EQ-5D-5L, the differences between arms were significant using OAB-5D, with the combination arm reporting the highest rate of responders. Furthermore, on OAB-5D, baseline to EoT changes in OAB-5D scores for all three treatments exceeded all the MIDs used.

Study strengths include the fact that the data are derived from a large randomized controlled Phase III trial and the use of well-defined health status utility measures. This is the first time MIDs have been calculated with the EQ-5D-5L value

set for England or with OAB-5D, though further studies are required to confirm these values. It should also be noted that these MIDs are specific to the value sets used to estimate utilities in the present study and they may not be transferable to other value sets or other patient populations. Further studies should also assess the impact of combination treatment on HRQoL in males, who were underrepresented in BESIDE, and to assess the impact of mirabegron with/without solifenacin on HRQoL in routine clinical practice.

5 CONCLUSIONS

In this analysis of data from the BESIDE trial, both preference-based health status measures analysed showed improvements from baseline to EoT in all three treatment arms. However, only the condition-specific measure showed a statistically significant benefit for combination treatment versus solifenacin monotherapy.

Using the more sensitive condition-specific OAB-5D instrument in combination with EQ-5D-5L makes it possible to evaluate the impact of treatment on dimensions of health status that are important to patients with OAB, while also permitting comparisons of outcomes from this study with different disease areas, in which EQ-5D-5L is used, that might be important for HTA decision-making. From a clinical perspective, use of combination treatment appears to be justified by gains in condition-specific HRQoL over and above those achieved with monotherapy.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002;21(2):167–78.

2. Tubaro A. Defining overactive bladder: epidemiology and burden of disease. *Urology.* 2004;64(6 Suppl):2–6.

3. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003;20(6):327–36.

4. Nicolson P, Kopp Z, Chapple CR, Kelleher C. It's just the worry about not being able to control it! A qualitative study of living with overactive bladder. *Br J Health Psychol.* 2008;13(Pt 2):343–59.

5. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. *BJU Int.* 2008;101(11):1388–95. doi: 10.1111/j.1464-410X.2008.07601.x.

6. Tang DH, Colayco DC, Khalaf KM, Piercy J, Patel V, Globe D, et al. Impact of urinary incontinence on healthcare resource utilization, health-related quality of life and productivity in patients with overactive bladder. *BJU Int.* 2014;113(3):484–91. doi: 10.1111/bju.12505.

7. Sadananda P, Drake MJ, Paton JF, Pickering AE. A functional analysis of the influence of beta3-adrenoceptors on the rat micturition cycle. *J Pharmacol Exp Ther.* 2013;347(2):506–15. doi: 10.1124/jpet.113.207340.

8. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, et al. Randomized double-blind, active-controlled Phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. *Eur Urol.* 2013;63(2):296–305. doi: 10.1016/j.eururo.2012.10.048

9. Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, et al. Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian Phase 3 trial. *Eur Urol.* 2013;63(2):283–95. doi: 10.1016/j.eururo.2012.10.016

10. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized Phase III trial of mirabegron in patients with overactive bladder. *J Urol.* 2013(4);189:1388–95. doi: 10.1016/j.juro.2012.10.017

11. Astellas Pharma US I. MYRBETRIQ Prescribing Information. Available at: https://www.us.astellas.com/docs/myrbetriq-full-pi.pdf. Revised June 2012. Accessed 22 June 2016.

12. Maman K, Aballéa S, Nazir J, Desroziers K, Neine ME, Siddiqui E, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol.* 2014;65(4):755–65. doi: 10.1016/j.eururo.2013.11.010.

13. Sexton CC, Notte SM, Maroulis C, Dmochowski RR, Cardozo L, Subramanian D, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. *Int J Clin Pract.* 2011;65(5):567–85. doi: 10.1111/j.1742-1241.2010.02626.x.

14. Longworth L, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess.* 2014;18(8):1–224. doi: 10.3310/hta18090.

15. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/. Accessed 15 September 2016.

16. Young T, Yang Y, Brazier JE, Tsuchiya A, Coyne K. The first stage of developing preference-based measures: constructing a health-state classification using Rasch analysis. *Qual Life Res.* 2009;18:253–65. doi: 10.1007/s11136-008-9428-0.

17. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011(10);20:1727–36.

18. Drake MJ, Chapple C, Esen AA, Athanasiou S, Cambronero J, Mitcheson D, et al. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised double-blind multicentre

Phase 3b study (BESIDE). *Eur Urol.* 2016;70(1):136–45. doi: 10.1016/j.eururo.2016.02.030.

19. MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, et al. Mirabegron as add-on treatment to solifenacin in incontinent overactive bladder patients with an inadequate response to solifenacin monotherapy: responder analyses and patient-reported outcomes from the BESIDE study. *J Urol.* 2016;196(3):809–18. doi: 10.1016/j.juro.2016.03.174

20. Devlin N, Shah K, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. Office of Health Economics. Research paper 16/01. Available at: https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england. Accessed 22 June 2016.

21. Feng Y, Devlin N, Shah K, Mulhern B, Van Hout B. New methods for modelling EQ-5D-5L value sets: an application to English data. Office of Health Economics. Research paper 16/02. Available at: https://www.ohe.org/publications/new-methods-modellig-eq-5d-5l-value-sets-application-english-data. Accessed 22 June 2016.

22. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res.* 2002;11(6):563–74.

23. Yang Y, Brazier J, Tsuchiya A, Coyne K. Estimating a preference-based single index from the Overactive Bladder Questionnaire. *Value Health.* 2009;12(1):159–66. doi: 10.1111/j.1524-4733.2008.00413.x.

24. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10(4):407–15.

25. Luo N, Johnson J, Coons SJ. Using instrument-defined health state transitions to estimate minimally important differences for four preference-based health-related quality of life instruments. *Med Care.* 2010;48(4):365–71.

26. Pavesi M, Devlin N, Hakimi Z, Nazir J, Herdman M, Hoyle C, et al. Understanding the effects on HR-QoL of treatment for overactive bladder: a detailed analysis of EQ-5D clinical trial data for mirabegron. *J Med Econ.* 2013;16(7):866–76. doi: 10.3111/13696998.2013.802240.

27. Desroziers K, Aballéa S, Maman K, Nazir J, Odeyemi I, Hakimi Z. Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder. *Health Qual Life Outcomes.* 2013;11:200. doi: 10.1186/1477-7525-11-200.

28. Heisen M, Baeten SA, Verheggen BG, Stoelzel M, Hakimi Z, Ridder A, et al. Patient and physician preferences for oral pharmacotherapy for overactive bladder: two discrete choice experiments. *Curr Med Res Opin.* 2016;32:787–96. doi: 10.1185/03007995.2016.1142959.

29. Swinburn P, Lloyd A, Ali S, Hashmi N, Newal D, Najib H. Preferences for antimuscarinic therapy for overactive bladder. *BJU Int.* 2011;108(6):868–73. doi: 10.1111/j.1464-410X.2010.09882.x

30. Kim A, Lee KS, Jung R, Na S, Kim JC, Kim HG, et al. Health related quality of life in patients with side-effects after antimuscarinic treatment for overactive bladder. *Low Urin Tract Symptoms.* 2016 Jun 12. doi: 10.1111/luts.12132.

Figure Legends

Fig 1 Mean scores in EQ-5D-5L (A) and OAB-5D (B) indexes from baseline to EoT in the mFAS.

Patient numbers at baseline* and EoT‡; compared with combination§.

EoT, end of treatment; *mFAS*, modified full analysis set (randomized patients [after 4-week solifenacin run-in] who received ≥1 dose of study treatment and completed the EQ-5D-5L questionnaire at baseline and at least once post-baseline).

Fig 2 Proportion of patients with no problems on the EQ-5D-5L (A) and OAB-5D (B) dimensions at baseline and at EoT in the mFAS.

Patient numbers at baseline* and EoT‡.

EoT, end of treatment; *mFAS*, modified full analysis set (randomized patients [after 4-week solifenacin run-in] who received ≥1 dose of study treatment and completed the EQ-5D-5L questionnaire at baseline and at least once post-baseline).

Table 1 Summary of demographics and baseline characteristics in the mFAS

	Combination (*n* = 694)	Solifenacin 5 mg (*n* = 684)	Solifenacin 10 mg (*n* = 676)
Sex, female (%)	83.3	83.0	83.9
Age, years, mean (SD)	58.2 (13.1)	56.8 (13.3)	57.4 (13.2)
Mean duration of OAB, months (SD)	76.5 (86.7)	67.5 (71.4)	70.8 (77.7)
No. of incontinence episodes during 3-day diary, mean (SD)	9.5 (8.7)	9.3 (8.2)	9.9 (9.2)
No. of incontinence episodes/24 hour, mean (SD)	3.19 (2.95)	3.14 (2.75)	3.32 (3.06)
No. of micturitions/24 hour, mean (SD)	9.12 (2.76)	8.89 (2.72)	8.99 (2.76)
No. of urgency incontinence episodes/24 hour, mean (SD)	2.84 (2.72)	2.77 (2.53)	2.88 (2.77)
No. of pads/24 hour, mean (SD)	1.95 (2.38)	1.90 (2.36)	2.06 (2.58)
No. of urgency episodes (grade 3 or 4)/24 hour, mean (SD)	5.74 (3.83)	5.57 (3.60)	5.67 (3.78)
No. of nocturia episodes/ 24 hour, mean (SD)	1.15 (1.13)	1.07 (1.03)	1.15 (1.11)

mFAS, modified full analysis set, *FAS* (randomized patients [after 4-week solifenacin run-in] who received ≥1 dose of study treatment and completed the EQ-5D-5L questionnaire at baseline and at least once post-baseline); *OAB*, overactive bladder; *SD*, standard deviation.

Table 2 Responder analysis for EQ-5D-5L and OAB-5D at EoT in the mFAS

	Responder definition of MID	Combination (*n* = 694)	Solifenacin 5 mg* (*n* = 684)	Solifenacin 10 mg* (*n* = 676)
Single responders				
EQ-5D-5L	≥0.102	27 %	26 % *p* = 0.75	25 % *p* = 0.68
	≥0.065	37 %	34 % *p* = 0.54	32 % *p* = 0.19
	≥0.017	50 %	46 % *p* = 0.28	45 % *p* = 0.27
OAB-5D	≥0.043	77 %	66 % *p* < 0. 01	66 % *p* < 0. 01
	≥0.020	84 %	77 % *p* < 0.01	77 % *p* < 0.01
	≥0.054	74 %	62 % *p* < 0. 01	62 % *p* < 0. 01
Double responders				
EQ-5D-5L OAB-5D	≥0.017 ≥0.054	40 %	34 % *p* = 0.03	33 % *p* = 0.02
EQ-5D-5L OAB-5D	≥0.017 ≥0.043	42 %	36 % *p* < 0.05	35 % *p* = 0.03
EQ-5D-5L OAB-5D	≥0.017 ≥0.020	45 %	39 % *p* = 0.10	39 % *p* = 0.08
EQ-5D-5L OAB-5D	≥0.102 ≥0.054	23 %	20 % *p* = 0.23	20 % *p* = 0.23
EQ-5D-5L OAB-5D	≥0.102 ≥0.043	24 %	21 % *p* = 0.29	20 % *p* = 0.29
EQ-5D-5L OAB-5D	≥0.102 ≥0.020	25 %	23 % *p* = 0.60	23 % *p* = 0.52
EQ-5D-5L OAB-5D	≥0.065 ≥0.054	31 %	26 % *p* = 0.07	25 % *p* = 0.03
EQ-5D-5L OAB-5D	≥0.065 ≥0.043	32 %	27 % *p* = 0.12	25 % *p* = 0.03
EQ-5D-5L OAB-5D	≥0.065 ≥0.020	34 %	30 % *p* = 0.27	28 % *p* = 0.07

*, adjusted *P*-values for combination therapy compared with solifenacin monotherapy.
EoT, end of treatment; *mFAS*, modified full analysis set (randomized patients [after 4-week solifenacin run-in] who received ≥1 dose of study treatment and completed the EQ-5D-5L questionnaire at baseline and at least once post-baseline); *MID*, minimally important difference.